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Patient and carer views on participating in clinical trials for prodromal Alzheimer's disease and mild cognitive impairment

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Abstract

There is great interest in conducting clinical trials of disease-modifying therapies in the prodromal (early, pre-dementia) or even in the asymptomatic stages of AD. For potential participants, deciding whether to take part in a clinical trial is a complex process in which risks and discomforts must be balanced against uncertain benefits, particularly in the context of potentially serious adverse events. Focus groups with people with early memory problems, current and former family carers explored attitudes towards participating in clinical trials in the prodromal stages of the disease, using an example of anti-amyloid antibody-therapy (immunotherapy) which are currently in development. Despite the complexities involved, almost all participants had a clear idea about whether they, personally, would like to take part. Many were highly motivated to find out more about the underlying cause of their memory problem, regardless of their desire to participate in a clinical trial. Participants expressed minimal concern regarding the risk of adverse events associated with immunotherapy, whereas certain tests and trial procedures provoked greater anxiety. People with memory problems were found to assess the study demands in relation to their own priorities and circumstances. These findings can be used to inform the ethical debate around the disclosure of biomarker status, the design of clinical trials and the content of trial information.

INTRODUCTION

Dementia affects an estimated 24 million people worldwide, the majority of whom will have Alzheimer's disease ¹. Currently, there are no effective treatments and some of the most promising disease-modifying compounds have failed to show efficacy in phase III drug trials, despite promising pre-clinical data ². An often cited reason for this is that in the mild to moderate dementia stage of AD, when the drugs have been traditionally tested, the underlying pathology in the brain is at an advanced and irreversible state ^{3 4 5}. Hence, there is significant interest in conducting clinical trials earlier in the disease course, particularly at stage of Mild Cognitive Impairment (MCI) before the onset of dementia including significant functional impairment and when the pathology may be less advanced and modifiable. Diagnostic biomarker tests now allow for detection of Alzheimer's pathology in patients with MCI, with high (but not absolute) accuracy ⁶⁻⁸, paving the way for identifying prodromal AD patients to participate in clinical trials that may slow or halt progression to the clinical symptoms of dementia.

One promising avenue for drug development has been antibody therapies raised against amyloid- β peptide (A β). Several phase II trials of different anti-amyloid antibodies under development have shown they can reduce A β levels in mild to moderate AD ⁹⁻¹¹ and have a safety profile supporting their progression to efficacy phase III trials, the first of which should be completed in 2012 (clinicaltrials.gov). However, participating in an immunotherapy clinical trial is an extensive undertaking involving multiple medical examinations, regular injections, MRI and lumbar punctures over several years. Whether an individual will derive benefit from the drug is unknown and immunotherapies have been found to be associated

with significant side effects, including pain or allergic reactions where the injection is given and, in 5-10% of people, potentially more serious adverse events including vasogenic edema and microhemorrhages ⁶. For trials of patients with MCI there is the additional uncertainty surrounding their diagnosis, before it is clear whether it is prodromal AD. Researchers and clinicians have only just begun to address the critical ethical considerations surrounding the use of biomarkers for early detection and diagnosis ¹³. To date, no study has explored how people with mild memory complaints themselves may feel about learning their biomarker status within the context of a clinical trial. We sought to explore this key issue using an example of an immunotherapy clinical trial, due to it being topical and having a complex risk to benefit profile.

A favourable risk-benefit ratio is an ethical requirement for clinical research; not only must risks be minimised and potential benefits enhanced, but the potential benefits to individuals and the knowledge gained for society must also be considered to outweigh the risks, including considerations such as the strength of evidence from preliminary trials. However, these variables are difficult to quantify and there is no accepted formula to determine whether the potential benefits “outweigh” the risks ¹². It is vital that the views of people with memory complaints and their families are at the centre of informing ethical debate and procedure pertaining to these key issues.

METHODS

We conducted a series of focus groups to explore the level of risk that people with memory problems and family carers would be prepared to take to gain benefit from potential new therapies in a clinical trial setting. This allowed us to examine the perceived acceptability,

feasibility and conduct of future clinical trials in this area ¹⁴. Favourable ethics permission for the study was obtained from the London Central NRES Committee.

Participants

In accordance with the design of immunotherapy clinical trials, participants included people that have a diagnosis of Mild Cognitive Impairment (MCI) and close relatives. The views of former carers of people with Alzheimer's disease were also sought to explore how this experience might influence attitudes towards trial involvement. Participants were recruited through the Alzheimer's Society Research Network and an Alzheimer's Society run peer support project for people with mild memory complaints. Individuals attending the support group could only do so via referral from a local memory service and therefore had been assessed by a Consultant as having a 'mild memory complaint'. Efforts were made to recruit participants with a variety of socio-demographic characteristics, including age, gender, ethnicity and relationship to the person with memory problems, so we were able to investigate how individuals weigh up the perceived risks and benefits of participating in an immunotherapy clinical trial from a range of perspectives (see Table 1). The discussion groups continued until data saturation was achieved and no new themes were emerging from the data analysis.

Data Collection

Focus groups were used to help participants explore and clarify their views and provide insight into the decision making process ¹⁵. Participants were sent a briefing document in advance of the focus group to allow them time to consider the issues. A member of the research team knowledgeable about clinical trials in dementia provided a short presentation summarising what participation in an immunotherapy clinical trial might involve and answered all technical questions, which allowed the discussion to progress. At the time of conducting the focus groups, no clinical trials were actively recruiting prodromal patients in the UK. Therefore discussions focussed on a hypothetical trial of immunotherapy for people

with mild memory problems, based on published and unpublished trial protocols. Topics of investigation included: whether individuals would be prepared to participate in an immunotherapy clinical trial; the main areas of concern; whether individuals would want to learn that their memory impairment had a likely underlying Alzheimer's pathology; whether the potential benefits of the therapy justify the risks involved; and areas of misunderstanding or confusion where better information is needed. The topic guide was amended iteratively and aimed to follow the participants' own concerns. Each focus group lasted approximately 90 minutes, was audio-recorded and transcribed verbatim.

Data Analysis

A systematic analysis procedure, based upon principles of grounded theory¹⁶, was used to generate an increased understanding of how participants weigh up the possible risks and benefits of an immunotherapy clinical trial. Grounded theory is primarily inductive, and themes are derived from the data rather than from existing theory. Data collection and analysis proceeded simultaneously and emerging themes were tested out in subsequent discussion groups, for example, the suggestion that participation in a clinical trial could "upset the balance" was explored in later groups. Two of the research team (VL, JM) read through each focus group transcript independently and identified and labelled the data with descriptive codes. They then compared their coding strategies and discussed any instances of disagreement until a consensus was reached. One researcher (VL) then used the "constant comparison" method to delineate the similarities and differences between the codes to enable a final coding framework to be developed. Codes were grouped together to form higher level conceptual categories, which were verified and refined as the analysis proceeded. The transparency of the research process was increased through theoretical memos, which documented thoughts, interpretations and questions about the data, the on-going development of categories and their relationships¹⁶.

RESULTS

Twenty-eight participants took part in 4 focus group discussions (focus group 1: $n = 1$ person with memory problems, 2 carers, 6 former carers; focus group 2: $n = 2$ people with memory problems, 4 carers; focus group 3: $n = 4$ people with memory problems; focus group 4: $n = 7$ people with memory problems, 2 carers). A range of strongly defined views emerged across the groups that provided insight into: the perceived benefits of the screening process and study drug; the demands of taking part; attitudes towards side effects; information needs and the decision making process (see Table 2). These themes will now be discussed in depth.

Attitudes towards the screening process

Perceived benefits of the screening process

One of the most prominent themes to emerge in the focus group discussions was the sense of uncertainty surrounding the cause of individual's memory problems. Participants sought clarification regarding whether they could be a side effect of medication or other physical conditions or a consequence of age, depression, anxiety or, as feared by many, dementia. People with memory problems and current carers indicated that one of their primary motivations for getting involved in the clinical trial would be to find out whether the person's memory problems had an underlying Alzheimer's pathology.

Lillian: I would rather know.

Janet: Could you deal with it Lillian?

Lillian: I could deal with it. I have dealt with a lot in my life, so it would be just another thing for me to deal with, and I would rather deal with it than not know and then all of sudden realise I am not well. And I feel sure about that.

Julie: Because I am, sorry, but younger than most people here [laughter] I would want to know and then if I could do anything myself to improve my memory, that would help.

(Group 4)

Stigma of dementia

Here the comments of people with memory problems and current carers contrasted with those of former carers who expressed strong reservations about whether they personally would want to address cognitive difficulties at that early stage. Former carers were alone in discussing issues of stigma and the unwelcome practical and emotional implications that receiving a diagnosis might hold. They acknowledged that it was difficult for them to put their extensive experience of Alzheimer's disease to one side. Former carers were more likely to construe participation in terms of the potential benefits for future generations and society as whole. While other participants recognised that taking part in a trial of this sort could benefit others, this was not in itself considered an adequate reason to get involved. Individuals were clear that first and foremost it would have to be the right decision for them.

Perceived benefits of study drug

There was a strong impression across the focus groups that participants assumed the study drug would be beneficial and few sought information regarding the effectiveness of the intervention. Concerns related not to whether the study drug would work, but the risk of being randomised to the control group and of receiving the 'dummy' drug instead. Participants explained that this would leave them feeling angry and disappointed. Yet it was also evident that the vast majority of participants both understood and accepted that the intervention did not promise to improve their cognitive state but simply to limit further deterioration. There was a consensus that maintaining their current condition would be benefit enough.

Josephine: You know I check and double check to make sure everything is written down, so if I can just maintain where I am. That would be great too if I get better, you know.... but as long as I know it's not going to be worse than what I am getting now. (Group 2)

Former carers concurred that even modest benefits would be worth an enormous amount.

Mary: My feeling would be if the quality of life was marked and obvious, even for 3 months, I know my husband would have snatched it off a tree. (Group 1)

In the majority of instances the perceived benefits of the intervention itself did not present as a decisive factor in the decision making process. Rather participants seemed to concentrate on whether the person with memory problems was eligible for the trial and / or whether they could tolerate the demands of taking part. If these criteria were satisfied, *any* chance of improvement seemed to merit participation.

Jim: My view is I'd like the option, obviously. It's like the lottery, 'if you aren't in it you can't win it'. (Group 4)

Demands of taking part

Certain tests and procedures involved in the trial, particularly lumbar punctures and MRI scans, provoked widespread anxiety. There was also a large number of questions regarding whether the study drug would be compatible with medication that participants were already taking. Whether the study demands were construed as off-putting or tolerable seemed in part to reflect how concerned participants were about their cognitive or their physical condition. Some participants spoke at length about the negative impact of memory problems on their lives. These individuals, along with the majority of current carers in the focus groups, were highly sensitive to changes in the individual's cognitive state and feared

progressive deterioration. These participants seemed prepared to endure invasive tests in the hope that they might find out more about the underlying cause of their complaint. They also indicated that they would accept the on-going demands of participating in the clinical trial if they were considered eligible to take part.

Julie: It [lumbar puncture] was painful, very painful but not so painful that I would say, "Well I won't do the tests or anything". I would have another go.

Moderator: How do other people feel about doing those sorts of tests?

Margaret: I'm alright, I will do it.

Lillian: I'm alright with injections, I have had so many.

Kenneth: Like I said to you with the injection, it's worth a try if you are going to find out, you know what I mean? (Group 4)

Conversely, other older people emphasised that they were currently coping with their memory problems and frequently mentioned strategies such as making lists that helped them to live independently. Many of these participants were suffering from co-existing physical complaints that caused pain, discomfort and distress. Participating in a clinical trial was generally considered too demanding in this context.

Ivy: I don't feel very safe with any more treatment for anything, because I had a back operation 3 years ago, I had, I can't remember what you call it, but it was the arthritis and everything and then the hip, and I am still in a lot of pain, so I just decide to go through with whatever happens to me now. No more, I am managing fine as it is. (Group 4)

While these participants they were not opposed to finding out more about their condition, they stated that they were not prepared to put their wider health at risk to do so. Maintaining the fine balance that they had achieved in managing their medication, physical health and memory problems was considered to be of greater importance. There were few objections

to the actual time commitment that the clinical trial required, although a reoccurring issue related to the organisation of the appointments at the study centre. These had to accommodate other commitments, particularly for 'study partners' (family members) who were likely to be working.

Caroline: The thing is if it's once a month is it on a specific day each month, because for us, some of us are working and we would need to take those days off work in order to accompany our parents. Is it on a regular day, like you know with the meetings? Because we know it is always the last Friday of the month, so at least we can organise our time off at work. (Group 2)

People with memory problems who were attending the focus group on their own gave mixed responses about who could act as a study partner and how feasible it would be for them to do so. Some participants were confident that this would not be a problem; others were clearly worried about burdening their relatives.

Doris: Your children won't be able to go because they are busy. Your children they are busy with their households and demanding jobs, they won't be able to come. It will be difficult for them to attend. (Group 3)

Minimal concern about side effects

In contrast to the demands of taking part in the clinical trial, people with memory problems, past carers and current carers seemed largely unconcerned about the side effects that had been reported in previous studies. Former carers asked questions about the precise stage of current trials and how they were being monitored, yet the majority of participants displayed confidence that the drug must be sufficiently "safe" to have reached this stage in the development process. Moreover, there appeared to be a general acceptance that all

medications have associated certain side effects and may or may not be suited to the individual.

Dennis: All tablets are risk taking aren't they? I mean the doctor can look in her little book and say, "This is what I am giving you." They don't suit everyone do they? (Group 3)

Information needs

There was a consensus that additional information should be given about the role of study partner. People with memory problems were keen to find out who could perform this role and why it was necessary. Relatives sought clarification on how the appointments would be arranged and what procedures they should follow in certain scenarios e.g. if they observed side effects. Participants also thought it was important to find out where the trial would be based so that they could assess the feasibility of travelling to the centre. Family members asked a wide range of questions relating to the design of the trial such as how the study drug / placebo would be allocated and what would happen if their relative's cognition deteriorated during the trial period. Given the significance that participants attached to the screening process there was a strong feeling that the study information should specify more clearly what this would involve and how this would establish whether their relative was suitable to take part in the trial.

Caroline: I think we have asked a lot of questions about the tests and so on because it wasn't very clear that after you have had the lumbar and the brain MRI scans some people will actually be told "no, you can't take part" or "yes you can". (Group 1)

Finally, a couple of people with memory problems commented that they had found the study information difficult to retain. It was evident that in addition to written information both people with memory problems and family members required the opportunity to discuss their

questions and concerns with an informed member of the research team before they could commit to a trial of this sort.

Making the decision

Participants described a step-wise approach to the decision making process: first, they would undertake the 'screening' to gain a better indication of the underlying cause of memory problems; then, they would evaluate whether they wished to be involved in a trial.

Josephine: For me, for now it's the lumbar puncture and the MRI, that's the one important thing now and then when we know the results that's when the decision will come because then we will know exactly where we are. (Group 2)

For the most part, the people with memory problems in the focus groups expressed clear preferences about whether they would wish to take part in a clinical trial. Yet, the majority also agreed that they would only reach a decision after they had considered the issues with their families. While not all participants wished to take part themselves the groups were unanimous that clinical trials of this sort should be allowed to go ahead. The common view was that individuals must decide for themselves.

Maggie: You give people as much information as they can handle as the individual and the partner or the principal carer and you give them that information and you leave them to make informed choices. I don't think anybody else can make that choice for you. (Group 1)

DISCUSSION

There was recognition that the decision to participate in an immunotherapy clinical trial involved weighing up multiple factors, many of which were unknown. However, the majority

of participants seemed to have a clear idea about whether they, personally, would wish to take part. One of the primary findings was that people with memory problems and relatives appeared highly motivated to find out more about the underlying cause of the condition, regardless of their desire to participate in a clinical trial. The need for an unambiguous diagnosis frequently dominated the discussion, while the potentially negative psychological and legal consequences of learning one's biomarker status¹⁹ were rarely touched upon. This is consistent with evidence that receiving a diagnosis of dementia can engender feelings of relief and reduce anxiety²⁰. Whilst the findings suggest that patients desire further information about their prognosis and cause of their memory impairment, there are still important ethical considerations for clinicians to ensure that appropriate support, services and counselling are available for patients undergoing tests for biomarker status. Sufficient time and attention must be given both to preparing participants for these results and the subsequent discussion of their implications¹³. The findings also highlight how difficult but crucial it is to explain to participants the level of uncertainty that remains regarding the likelihood of progressing towards Alzheimer's disease. While studies point towards the high diagnostic accuracy of biomarkers in Mild Cognitive Impairment²¹ participants need to understand that an enduring possibility of misdiagnosis¹⁹ remains.

It was apparent that participants were prepared to take part in the clinical trial if the study drug promised to maintain, as opposed to improve, their cognitive state. Participants indicated that *if* concerns around eligibility and study demands could be met *any* chance of accessing this benefit would merit participation. The findings suggest that patient perception of risks from participating in a clinical trial of immunotherapy may be different to that of clinicians and regulators. People with memory problems and carers expressed minimal concern regarding the risk of adverse events associated with immunotherapy⁶. Conversely some of the more invasive tests and procedures involved in the trial provoked anxiety across the groups as indicated in studies of well older adults²². Whether the study demands were construed as off-putting or tolerable seemed in part to reflect how concerned participants

were about their cognitive or their physical condition, again illustrating the highly personal nature of this decision. The findings support evidence that individuals with Alzheimer's disease remain able to meaningfully evaluate risk / benefit profiles, even in the face of decreased decisional abilities ¹⁷. They also suggest that concerns about exposing people with dementia to high levels of risk because of poor judgement ¹⁸ may be unwarranted.

The study also highlights the high level of comorbidity among the target group. In generating clinical trial literature, people with memory problems and their relatives require clear information regarding the exclusion criteria and whether comorbid medical conditions would prevent them participating. In addition to written information participants required the opportunity to discuss their questions and concerns with an informed member of the research team. Establishing a relationship of trust with the trial co-ordinators has been found to minimise concerns about potential risks in other studies ²³. There was little evidence of difference among the people with memory problems and relatives that attended the focus group together. Yet, people with memory problems that attended on their own expressed greater reservations about inconveniencing family members and whether they would be able to cope with participating in a clinical trial. This suggests the importance of consulting both the person with memory problems and his or her relative from the recruitment stage onwards, so that all parties have the opportunity to contribute their views.

Overall, this study highlights that the views and preferences of people with memory problems and their relatives can be used positively to inform the ethical debate around the disclosure of biomarker status, the design of clinical trials and the content of trial information. However, some caution should be used when interpreting the findings. The numbers involved in this qualitative study are limited and the views expressed may not be typical of people with Mild Cognitive Impairment or carers. Arguably, agreeing to participate in a focus group about immunotherapy clinical trials suggests a degree of interest in research and interventions that may not be shared by all. However, efforts were made to explore

differences of opinion and recruit participants from a variety of backgrounds, and ultimately a wide range of strongly defined views were articulated across the groups. Therefore we believe the findings have applicability beyond the context of this research and can help to move the ethical debate forward in this area.

TABLE 1: Demographic Characteristics of Focus Group Participants

Variable	Mean	Range
Age of person with memory problems (y)	69	45-86
Time since diagnosis (y)	1.9	1-4
	N (%)	
Type of participant		
Person with memory problems	14 (50)	
Current family carer	8 (29)	
Former family carer	6 (21)	
Gender of person with memory problems		
Female	6 (43)	
Male	8 (57)	
Relationship of carer to person		
Husband	4 (29)	
Wife	3 (21)	
Son	3 (21)	
Daughter	4 (29)	

TABLE 2: Summary of key themes

Category	Sub-category	Description
Attitudes towards the screening process	Perceived benefits of the screening process	<ul style="list-style-type: none">• The 'screening' stage was identified as one of the primary benefits of participating in the trial; participants were keen to know the cause of their condition and what the future may hold.• Potential benefits to society were recognised, but were generally not considered reason enough to participate in a clinical trial.
Perceived benefits of study drug	Stigma of dementia	<ul style="list-style-type: none">• Former carers were alone in expressing concern about being labelled with "dementia".• The majority of participants appeared to assume that receiving the study drug would be beneficial.• There was a consensus that limiting further cognitive deterioration was sufficient benefit.• Receiving the placebo was considered a highly undesirable outcome.
Demands of taking part	Widespread concern	<ul style="list-style-type: none">• The use of MRI scans and lumbar punctures provoked anxiety across the groups.• Whether the study demands were construed as off-putting or tolerable in part reflected how concerned participants were about their cognitive or their physical condition.
	Tolerable 'v' off-putting	<ul style="list-style-type: none">• Some participants spoke at length about the negative impact of their memory problems on their lives. Many feared that they would get progressively worse and were keen to be involved in a clinical trial.• Others appeared more preoccupied with physical complaints, which had often caused pain, discomfort and distress. They feared that taking part in a clinical trial might upset their balance in managing their medication, physical health, and memory problems
Attitudes towards side effects Information needs	Limited concern	<ul style="list-style-type: none">• General acceptance that all medications / treatment have associated side effects.• Assumption that drug must be sufficiently "safe" to have reached this stage.• Further information was considered necessary regarding the precise role of the "study partner".• Further information should be given about the design of the trial, in particular, the 'screening' and how suitability would be established.
Making the decision	Step wise approach	<ul style="list-style-type: none">• Participants required both written information and the opportunity to discuss questions and concerns.• Participants described, first, undertaking the 'screening' to gain a better indication of the underlying cause of memory problems and subsequently evaluating whether they wish to be involved in a trial.
	Joint decision with family	<ul style="list-style-type: none">• People with memory problems expressed clear preferences about participating in a clinical trial, but agreed that it would have to be a joint decision with their family.

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